REMARKS

Upon entry of the amendments, claims 1-42 constitute the pending claims in the present application. Among them, claims 19-39 are withdrawn from further consideration by the Examiner as being drawn to non-elected inventions. Applicants will cancel these claims upon indication of allowable subject matter. Claims 1-18, 40, 41, and new claim 42 constitute claims currently being considered by the Examiner.

The Office Action has indicated that Applicants' arguments and amendments filed in Paper No. 10 (2/1/02), and new formal drawing submitted in Paper No. 11 (1/16/02) are acknowledged. The Office Action has also stated that certain objections / rejections are withdrawn. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

Claim rejections under 35 USC §112, first paragraph

Claims 2, 4, 11, 15-16 remain rejected under 35 U.S.C. 112, first paragraph because the specification does not enable any person skilled in the art to practice the invention commensurate with the scope with these claims.

The Office Action states that claim 2 is overly broad because the term "substance" reads on a wide range of potential compounds that are encompassed by the claim. The Office Action argues that function alone does not enable a skilled artisan to make and use the "substance" because absent a correlative structure or guidance regarding the structures that would predictably have the desired effect, it would require undue experimentation to practice the full scope of the claimed invention. In other words, the Office Action alleges that the instant specification does not enable a skilled artisan to make and use any and all substances other than the ones already disclosed.

Applicants submit that the test for enablement is whether a skilled artisan, in view of the teaching of the specification, can make and use the claimed invention without undue

experimentation. Thus the question becomes whether the instant specifications teaches a skilled artisan *how to obtain* a substance capable of interfering tertiary complex formation, and if so, whether such experimentation is *routine or undue*.

Regarding the first part of the question, Applicants submit that the instant specification teaches in numerous occasions, and in sufficient detail, to enable a skilled artisan to identify / make such substance. For example, on page 12, lines 16-28; page 14, lines 7-22; and page 17, lines 23 to page 18, line 29, the specification teaches that the TRAP assay and/or the bone nodule formation assay can be used to screen for compounds that can disrupt the formation of the tertiary complex. Although the nature of the compounds to be screened can be quite diverse (for example, from natural or synthetic polypeptides to natural or synthetic chemical compounds, with or without defined structure or chemical property), as long as the methods taught by the instant specification can be used to screen such compounds to yield substance capable of inhibiting the tertiary complex formation, the method fulfills the first part of the requirement..

Contrary to the assertion of the Office Action, a skilled artisan would *not* need to known which classes of compounds / substances he should choose for the screen, because the type of substance is not a limitation of claim 2. In reality, the chemical nature and/or structure of compounds screened are frequently unknown in many (if not all) drug screening processes. In fact, it might even be desirable to screen as many different kinds of compounds, with known or unknown structure, as possible to obtain a substance useful for practicing the claimed invention.

Regarding the second part of the question, Applicants submit that such screen is merely routine in drug discovery business, where millions, if not hundreds of millions, of compounds are routinely obtained and screened, typically spanning a long period of time and involves large amount of labor and capital investment, and thus such screen does not constitute undue experimentation. Neither does a high rate of failure or low predictability of success alone entails the experimentation "undue." To support these views, Applicants wish to draw the Examiner's attention to several controlling cases regarding what amount of experimentation is reasonable rather than undue.

In *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 231 USPQ 81 (Fed. Cir. 1986), CAFC rules that "the trial court erred in finding a lack of enablement for failure to set forth

the methods of making monoclonal antibodies and of screening for proper antibodies. The evidence indicated that both methods were known to person skilled in the art." Therefore, simply setting forth a screen method to obtain a substance (monoclonal antibody / "substance") with a desired function (binding a specific antigen / interfere tertiary complex formation), even though the well-known methods (making and screening for monoclonal antibody) are not explicitly disclosed in the application, is enabling for those substances that are not yet obtained, but nevertheless can be obtained if the methods taught by the specification are followed. Since "a patent need not teach, and preferably omit, what is well know in the art."

Neither does the screen method need to be a *foolproof* one. In other words, the taught method need not be one that will guarantee a high rate of success. In *Johns Hopkins University v. Cellpro., Inc.*, 152 F.3d 1342, 47 USPQ2d 1705 (Fed. Cir. 1998), the patentee claims a genus of monoclonal antibodies specific for a weak antigen CD34, while showing only one working monoclonal antibody. The accused infringer argues that the patentee does not enable a skilled artisan to make any antibodies other than the one shown. The CAFC rules that the claim in question is enabled, even though the laboratory of one of the named inventors failed to produce a second antibody falling within the scope of the claimed invention after a "major effort." The Court states that "[I]t is imperative when attempting to prove lack of enablement to show that one of ordinary skill in the art would be unable to make the claimed invention without undue experimentation." Regarding what constitutes undue experimentation, there are two sources that could contribute to the amount of experimentation. One source arises from the intrinsic nature of the problem to be solved, in that case, to obtain a monoclonal antibody specific for an intrinsically weak antigen CD34. Indeed, one expert witness of the infringer testified that it was generally "more difficult" for him to produce a CD34 antibody than other monoclonal antibodies, and he attributed this difficulty to the weak immunogenicity of the source antigen. The other source comes from the fact that the patent disclosure is insufficient so that a skilled artisan could not, even when properly following the guidance of the specification, make and use the claimed invention, thus leading to undue experimentation by the skilled artisan. The Court rules that since the expert "explained that the relative difficulty that was encountered in producing CD34 antibodies may have been due to the weak immunogenicity of the KG-1a cell line, ... not because of an insufficiently enabling disclosure," this "suggests that the Kohler/Milstein technique was not foolproof, and that success with this technique commonly required repetition. This lack of

certainty was thus not attributable to a failure of disclosure in the '204 patent" (emphasis added). Clearly, the amount of experimentation is only undue if the skilled artisan has to engage in experimentation to compensate "an insufficiently enabling disclosure," but not when the specification has disclosed everything a skilled artisan needs to know to carry out the experiment, even if the amount of such experiment is routinely large.

Similarly, Applicants submit that the instant specification discloses at least two screen methods that can be used to obtain the substance of the claimed invention, just like a skilled artisan would be able to obtain the CD34 antibody if he follows the disclosure of the "'204 patent." The screen process may even be tedious and with unpredictable success rate due to the nature of the problem, just like the screen for CD34 antibody. But since the instant specification has provided numerous successful working examples including very small peptides to large antibodies, which is much more than the single working example in the "'204 patent," a skilled artisan would be convinced that more of such substances may exist and could be identified through routine experimentation. On the contrary, the Office Action has failed to show why one of ordinary skill in the art would be unable to make the claimed invention without undue experimentation, and that the amount of experimentation is due to insufficient disclosure of the specification rather than the nature of the problem to be solved.

The Office Action also asserts that recitation of "mutant IL-11R" in claim 4 is overly broad because the instant specification does not provide sufficient guidance to render it predictable which mutations in any other region of the receptor would predictably share the instant activity.

Applicants submit that the predictability issue does not appear to be relevant in the instant case. Predictability issue could arise if Applicants have only shown that a few mutant IL-11R is effective in interfering the formation of the tertiary complex, and claims that all other mutant IL-11R, without specifying the nature of these mutations, are also effective in interfering the formation of the tertiary complex. Such is not the case here. Instead of blindly claiming all other mutant IL-11R, dependent claim 4 still carries the limitation of claim 2 that the mutant IL-11R inhibits tertiary complex formation *in vivo*. As argued above, Applicants submit that the instant specification has taught a skilled artisan how to make and use any substance that can inhibit the

formation of tertiary complex without undue experimentation. See, for example, page 9, 1st full paragraph for mutant IL-11R screening. In addition, the specification has pointed out on page 7, lines 29-31 that "*mutations in other regions of the IL-11R protein can alter the characteristics of the gp130 binding site on IL-11R and prevent or inhibit productive IL-11R / gp130 interaction.*" As argued above, all that is needed to identify such mutant IL-11R protein is a random / combinatory mutagenesis procedure (which is well-known in the art at the time of filing, see response to the previous Office Action), coupled with screen assays such as those taught by the instant specification. However, contrary to the assertion of the Office Action, a prediction of which mutations in any other regions of the receptor that would be predictably share the instant activity is not required, since this predictability is related to the nature of the problem to be solved. The specification only becomes non-enabling for these mutant IL-11R proteins if the specification does not disclose sufficient information for carrying out the screen, but does not become non-enabling because it may be unpredictable as to whether additional mutant IL-11R can be identified, either in the same gp130 binding region or other different regions.

In addition, Applicants have amended claims 5-9 to further clarify the subject matter claimed. Amended claim 8 now depends on claim 4, while amended claims 5-7 and 9 are multiple dependent claims depending on claims 4 and 8. Applicants submit that claim 8, which is directed to soluble mutant IL-11R which inhibits, *in vivo*, the formation of a tertiary complex of IL-11, IL-11R, and gp130, is enabled to its full scope. Applicants have identified the region involved in IL-11R and gp130 binding, thus enabling the identification of additional similar mutations in the same region using art-recognized methodology such as random mutagenesis coupled with functional assays. Furthermore, Applicants have provided several working examples describing the exact soluble mutant IL-11R's that can be used to inhibit the formation of the tertiary complex. A skilled artisan, in view of the state of the art and the disclosure of the instant application, would be able to make and use such soluble mutant IL-11R without undue experimentation.

The Office Action also asserts that the recitation of "an IL-11 binding peptide" in claim 11 is only enabled for SEQ ID NOs. 1, 6, and 9, but not for other structures that can be readily identified by TRAP assay.

As argued above, the instant specification has provided sufficient disclosure for identifying additional substances that would be useful for practicing the claimed invention. In view of the several small peptides already identified by the assay methods, it only takes routine experimentation to identify more of similar peptides. As the Court states, "[I]t is imperative when attempting to prove lack of enablement to show that one of ordinary skill in the art would be unable to make the claimed invention without undue experimentation." The already identified peptides serves as proof that a skilled artisan would be able to make the claimed invention without undue experimentation. The burden is on the Examiner to provide convincing evidence or reasoning to show why these methods would not yield additional peptides of similar function, rather than for the Applicants to provide further working examples.

In addition, Applicants have amended claim 13 and added new claim 42 to further clarify the subject matter claimed. Amended claim 13 and new claim 42 recite several additional working examples of IL-11 binding peptides. Notably, SEQ ID NO: 5 and SEQ ID NO: 6 are tested to be effective to inhibit tertiary complex formation (see, for example, pages 9-11). SEQ ID NO: 10 differs from the human sequence (SEQ ID NO: 5) by just one amino acid, and is from the murine homolog of IL-11R. Although it has not been directly tested in an assay, given the identical biological functions in human and mouse, murine IL-11R most likely uses the same region to bind IL-11, and thus SEQ ID NO: 10 is almost certainly expected to have the same antagonizing effect. It naturally follows that their consensus, SEQ ID NO: 7, is also effective. The same argument applies to directly tested human sequence of SEQ ID NO: 6, its murine counterpart SEQ ID NO: 8, and their consensus SEQ ID NO: 9.

The Office Action also asserts that the recitation of "a small molecule" in claim 14 is too broad in that the nature of such a small molecule is left open for determination by the skilled artisan. As argued before, the nature of the small molecule is irrelevant since any compound can be screened by the method taught. The fact that several identified small peptides fall within the scope of the "small molecule" is evidence that such small molecules do exist, and additional ones can be obtained using the same or similar methods known in the art. As long as the specification provides enough detail to identify such small molecules without undue experimentation, the

specification has met the enablement requirement. In fact, the structure of many lead drug molecules identified in initial drug screens are unknown, even though it is known that these drug molecules do have the desired activity. And even if the structure is known, the functional moiety or group of that structure may still be unclear, and the art of rational drug design is devoted to the study of identifying such functional groups and optimizing these functional groups. Thus a skilled artisan could practice the claimed invention without knowing the basic chemical structure of the identified small molecule.

The Office Action also asserts that the recitation of "IL-11 antagonist" in claim 15 is overly broad in encompassing IL-11 mutants, or IL-11 antibodies, or short binding peptides (to) IL-11, or IL-11R binding peptides, etc. As argued above, to practice the claimed invention, a skilled artisan would not need to know a correlative structure of a potential IL-11 antagonist prior to the screen using an art-recognized or disclosed TRAP assay or bone nodule formation assay. The disclosure of the specification contains sufficient detail for a skilled artisan to conduct routine screening, just like in *Johns Hopkins University v. Cellpro., Inc.*, where sufficient details for screening for monoclonal antibodies specific for a given antigen are provided either in the specification or commonly available in the art. Therefore, no undue experimentation would have been required to practice the claimed invention, and the specification is enabling for claim 15.

The Office Action also asserts that the recitation of "IL-11R binding peptide" in claim 16 is overly broad, and a skilled artisan would not know which binding peptides to use for inhibiting the formulation of ternary complex absent of a correlative structure of what the antagonists are. As argued above, to practice the instant invention, a skilled artisan need only follow the guidance provided in the specification, namely to use the art-recognized or disclosed TRAP and/or bone nodule formation assay, to determine if any potential IL-11R binding peptide (such as given IL-11R antibody) is effective in blocking the formation of the ternary complex *in vivo*. This is much analogous to the *Johns Hopkins University v. Cellpro., Inc.* case mentioned above. Subsequent to the issuance of U.S. Pat. No. 4,965,204 (the "'204 patent" mentioned above), U.S. Pat. No. 5,035,994 ("the '994 patent"), directed to methods of using the monoclonal antibodies, was issued

from a divisional / continuation of the application giving rise to the '204 patent. Claim 1 of the '994 patent reads: "*1. A method of isolating a population of human cells containing pluripotent lympho-hematopoletic stem cells comprising: (a) providing a cell suspension from human tissue, said tissue selected from the group consisting of marrow and blood; (b) contacting said cell suspension with a monoclonal antibody to immature human marrow cells that is stage-specific and not lineage dependent so that said antibody binds to said stem cells, wherein said antibody specifically binds an antigen on human pluripotent lympho-hematopoletic stem cells said stem cells expressing an antigen that is specifically bound by the monoclonal antibody produced by the hybridomas deposited under ATCC Accession No. HB-8483 and does not specifically bind an antigen on mature, human myeloid and lymphoid cells; and (c) separating and recovering from said cell suspension the cells bound by said antibody, said bound cells being substantially free of nature lymphoid and myeloid cells*" (emphasis added). Thus, the claim recite a genus of monoclonal antibodies that can bind the same antigen bound by the only deposited monoclonal antibody. Although only one working antibody is identified by the taught screening method, the Court nevertheless holds that the antibody genus claim is enabled, because all a skilled artisan needs to know for a routine (yet laborious and difficult) screen is sufficiently disclosed. Although a skilled artisan may not know which other antibodies to use prior to the screening for more such monoclonal antibodies, only routine experimentation is required to identify such antibodies to practice the claimed invention. It naturally follows that a skilled artisan would be able to identify other IL-11R binding peptides according to the teaching of the specification using only routine experimentation.

In summary, based on facts and arguments presented above, Applicants submit that the specification is fully enabling for the invention as claimed. Even at the absence of certain structural information, a skilled artisan can still, and is actually encouraged, to screen a large number of compounds to identify other molecules suitable for practicing the claimed invention. Although the success rate may be unpredictable, Applicants submit that such unpredictability, if any, is not due to insufficient disclosure of the specification (which may constitute a basis for undue experimentation and non-enablement), but rather the specific nature of the problem to be

solved (which is not a basis for undue experimentation). Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. 112, first paragraph.

Claim rejections under 35 USC §112, second paragraph

The Office Action maintains the rejection of claim 1 under 35 U.S.C. 112, 2nd paragraph, for omitting a positive step for inhibiting the formation of a tertiary complex of IL-11 / IL-11R / gp130, because it is not clear as to what is to be done for achieving inhibition of complex formation. The Office Action alleges that a skilled artisan would not know what is to be administered to achieve the desired result.

Whether a skilled artisan would know what is to be administered to achieve the desired result (inhibiting ternary complex formation), i.e., how to practice the claimed invention, is an issue related to 35 U.S.C. 112, first paragraph, not second paragraph. Applicants submit that "one does not look to the claims but to the specification to find out how to practice the claimed invention" (MPEP 2164.08). The specification described in detail numerous ways of achieving the desired result, including (but are not limited to) administering mutant IL-11R, anti-IL-11 antibody, IL-11 binding peptide, small molecules, IL-11R binding peptides, specific anti-IL-11R antibodies, etc. Such embodiments are also claimed in dependent claims of claim 1. But regardless of these detailed descriptions and dependent claims, Applicants submit that claim 1 is not indefinite. There is no doubt as to the metes and bounds of the scope of claim 1, and a skilled artisan would readily and unequivocally recognize embodiments that fall within the scope of the claimed invention. The Office Action also fails to present a situation wherein it could be unclear whether certain embodiments would or would not fall within the scope of claim 1 due to the vagueness of the claim 1 language. Nevertheless, Applicants have amended claim 1 to further clarify the subject matter claimed. Amended claim 1 further clarifies a positive causal relationship between inhibiting the formation of the ternary complex and the intended result as stated in the preamble.

The Office Action also asserts that "neither is the mechanism by which the inhibition of complex formation is intended to be accomplished." If this can be interpreted to mean that Applicants should provide a mechanism of the claimed invention in the claim, Applicants submit

that there is no such requirement. In fact, pursuant to MPEP 2138.05, "[an] inventor need not understand precisely why his invention works in order to achieve an actual reduction to practice." It naturally follows that a patentable invention that has already been reduced to practice need not have a well-understood mechanism.

The Office Action also rejects claims 40 and 41 for reciting "bindings" rather than "binding." Accordingly, Applicants have amended these claims to correct these typographical mistakes.

In view of the amendments and arguments presented above, Applicants respectfully request that the Examiner reconsider and withdraw all rejections under 35 U.S.C. 112, second paragraph.

Claim rejections under 35 USC §102(b)

Claims 1-5, 10, 11, 15, 16, 40 and 41 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 9619574.

As mentioned before, Applicants have amended claim 1 to clarify the subject matter claimed. Applicants submit that WO 96/19574 does not anticipate the claimed invention because WO 96/19574 is non-enabled for the claimed *in vivo* treatment methods.

The claimed invention partly relies on the discovery that IL-11 exerts its effects on both bone resorption (likely through *activating* osteoclast function) and bone formation (likely through *inhibiting* osteoblast function). Therefore, inhibition of IL-11 signaling (for example, through inhibiting the formation of IL-11 / IL-11R / gp130 ternary complex formation) not only reduces bone resorption through inhibiting *osteoclast* function, but also promotes bone formation through eliminating the inhibitory activity of IL-11 on *osteoblast* (effectively activating osteoblast function). The net result is inhibited reduction of bone density, and in many desirable cases, even *increased* bone density in mammalian patients already suffering from bone loss (see page 4, 1st paragraph).

The Office Action alleges that WO 96/19574 provides the concept (paragraph bridging pages 6-7) and methods to achieve the results (Examples 1-3 in pages 22-29, and citations of other prior art in page 16, last paragraph). The relevant sentences in pages 6-7 reads, "*[m]ethods of inhibiting binding of IL-11 to the human IL-11 receptor in a mammalian subject are also disclosed which comprise administering a therapeutically effective amount of a composition containing a human IL-11R protein, an IL-11R inhibitor or an antibody to a human IL-11R protein. Methods of treating or preventing loss of bone mass in a mammalian subject using these compositions are also provided.*"

The test for enablement is whether a skilled artisan, in view of the disclosure of the specification, can practice the claimed invention without undue experimentation. Factors to be considered in assessing enablement is set forth in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), which includes state of the art, level of predictability, existence of working examples, amount of direction or guidance by the inventor, etc.

Applicants submit that WO 96/19574 never explicitly refer to the roles of osteoclasts or osteoblasts in bone density. Instead, WO 96/19574 merely vaguely mentions that "IL-11 and IL-11R may play a role in the regulation of bone maturation and repair" by citing several articles by Girasole et al., and Passeri et al. on page 16. As a skilled artisan would appreciate, bone density is determined by at least two counter-acting forces – osteoclast-stimulated bone resorption and osteoblast-promoted bone formation. At the time of filing of the instant application, many factors including IL-6, OSM, LIF, etc. (see page 2582, left column, 1st full paragraph of Romas et al.) are known to affect bone homeostasis by affecting at least osteoclastogenesis (and thus bone resorption). WO 96/19574 and its cited references at best discussed possible effects of IL-11 on osteoclast-stimulated bone resorption, based on *in vitro* data obtained from tissue culture cells. However, to reach the conclusion of WO 96/19574 that inhibiting osteoclast-stimulated bone resorption alone (using human IL-11R, IL-11R inhibitor, or anti-IL-11R antibody, etc.) is sufficient to prevent bone loss, at least two unstated and untested assumption has to be made. First, inhibiting IL-11 signaling have a) no effect at all on osteoblast-promoted bone formation; b) a stimulatory effect on osteoblast-promoted bone formation; or c) an inhibitory effect on osteoblast-promoted bone formation, wherein the extent of reduction in bone formation is less than the extent of reduction in bone resorption. Second, the effect of IL-11 on osteoclast and osteoblast are the

primary determinant of bone density *in vivo*. In other words, the effect of IL-11, on bone density *in vivo*, is so important that disruption of this effect can not be compensated by other factors having similar functions, thus causing a discernable change of bone density *in vivo*.

None of these two assumptions can be taken for granted based on *in vitro* data in the prior art before the filing of the instant Application. Regarding the first assumption, WO 96/19574 is completely silent about possible roles of IL-11 signaling in osteoblast. To obtain a complete picture of IL-11 signaling on bone density *in vivo*, a skilled artisan would thus need to investigate (at least *in vitro*) what effect IL-11 signaling might have on osteoblast (bone formation) before the artisan can follow the alleged invention of WO 96/19574. Since there is no disclosure as to whether osteoblast expresses IL-11R receptor, thus, based on the disclosure of WO 96/19574 alone, the artisan would need to engage in undue experimentation to determine whether osteoblast expresses IL-11R. Even if the artisan knows that IL-11R is indeed expressed in osteoblast in view of publications by Romas et al., the artisan would still need to conduct undue experimentation to determine whether IL-11 signaling affects osteoblast function *in vivo*, and if so, whether it stimulates or inhibits bone formation. The possible outcomes are highly unpredictable based on the disclosure of WO 96/19574 (see below), the state of the art, and level of skill in the art at the time of filing of the instant application.

Specifically, Example 2 of WO 96/19574 indicates that IL-11 signaling stimulates cell proliferation in cells expressing IL-11R. Thus, a skilled artisan, having known (through his own undue experimentation or through literature searching and reading Romas et al., etc.) that IL-11R is expressed on both osteoclast and osteoblast, would conclude that IL-11 can stimulate both bone resorption and bone formation. Thus it is highly unpredictable as to which one of these two counter-acting forces would prevail in the *in vivo* setting. Depending on the extent of stimulation, the net outcome could be any one of three possibilities: no change, loss of bone density, or increase of bone density.

The second assumption also can not be taken for granted. As stated above, there is a plethora of cytokines / growth factors that are known to be able to regulate at least one aspect of bone homeostasis, osteoclastogenesis. The disclosure of WO 96/19574, even when combined with that of Romas et al., at best suggest that IL-11 can also affect osteoclastogenesis. That result alone

does not make IL-11 any more important than any of the other previously mentioned cytokines for osteoclastogenesis under physiological conditions. Simply because a cytokine can perform a certain function in vitro, does not necessarily mean that the cytokine will perform that function in vivo. Even if does perform the same function in vivo, it can not be assumed that it is the sole or even a significant cytokine that performs that function in vivo. It is completely possible that IL-11 is capable of affect bone density, but only in such a minor role that eliminating this effect would have no discernable changes in overall bone density. Neither WO 96/19574 nor any of the cited references address this important issue. Given the unpredictable nature of the possible outcomes, the lack of guidance in the specification of WO 96/19574, the absence of even a single relevant *in vivo* or *in vitro* working example, and the lack of knowledge in the state of the art, a skilled artisan would be forced to perform undue experimentation to perform the alleged invention. Therefore, WO 96/19574 is non-enabling for treating or preventing bone loss by affecting IL-11 / IL-11R interaction in a mammalian patient.

In fact, Applicants submit that the disclosure of WO 96/19574 is inconsistent with, if not completely contradictory to, the notion that certain listed agents (such as those in pages 6-7) can be used to treat or prevent bone loss. The data presented, when viewed with other references (such as Romas et al.), create significant uncertainty as to the role of IL-11 on bone density *in vivo*. Thus, it does not enable a skilled artisan to practice the alleged invention.

For example, WO 96/19574 alleges that "*a therapeutically effective amount of a composition containing a human IL-11R protein, an IL-11R inhibitor or an antibody to a human IL-11R protein*" (emphasis added) can be used to inhibit IL-11 / IL-11R binding. However, since IL-11R is a membrane receptor protein (see Figure 1 of WO 96/19574), it is unclear whether such a membrane protein will be soluble and/or appropriate for direct administration; and even so, how such a protein can be functional without being inserted into the membrane.

Furthermore, even if it is construed that "IL-11R protein" refers to a soluble version (such as a fragment of the full-length protein), and assuming that such a soluble version of IL-11R can be used as described in Example 2 of WO 96/19574 to affect IL-11 signaling, such IL-11 signaling stimulates, rather than inhibits, proliferation of BAF130-9 cells, a derivative cell line of the pro-B cell line BAF/B03 (see page 24, line 17-18). Example 3 of WO 96/19574 also indicates that

soluble IL-11R can stimulate (normal) IL-11 signaling at the presence of IL-11 (see pages 27-29). The instant specification teaches that IL-11 has opposite effects on osteoclasts and osteoblasts (stimulates and inhibits, respectively). Thus, it is clear that the effect of IL-11 on different cell lines cannot be predicted without experimentation, even if the same ligands / receptor pairs are apparently involved. In view of this fact, a skilled artisan would not be able to predict if the soluble IL-11R will stimulate or inhibit the function of osteoclasts based on the disclosure of WO 96/19574 alone. Even if the artisan were to make a prediction based on the results of sIL-11R and IL-11 on BAF 130-9 cells in WO 96/19574, the artisan would have predicted that sIL-11R, when added to cells at the presence of IL-11 (as indicated on line 20 of page 24 to line 4 of page 25 in Example 2, and Figure 2), stimulates cell proliferation, thus *promotes*, rather than *antagonizes* IL-11 function. This data directly contradict the alleged invention (as claimed in claim 27 of WO 96/19574) that soluble IL-11R can be used to treat or prevent loss of bone mass (presumably through inhibiting IL-11 function). In fact, the instant specification confirms that such soluble IL-11R would not be able to inhibit IL-11 function. On page 29 (last paragraph of Example 4) of the instant specification, it is taught that a mutant IL-11R is capable of inhibiting IL-11-induced osteoclast formation, whereas the native IL-11R is not (also see and compare Figures 7A and B of the instant application). Thus, WO 96/19574 is non-enabling as to using a human IL-11R protein to treat or prevent bone loss.

In addition, regarding IL-11R inhibitor, aside from the reasons presented above as to why WO 96/19574 is non-enabling in general, there is an additional concern regarding this specific non-enabling embodiment. WO 96/19574 fails to disclose even a single working example of such an inhibitor. In fact, WO 96/19574 merely describes a very generic screen procedure for obtaining inhibitors of IL-11 / IL-11R binding (see page 6 and 14-15 of WO 96/19574). The Office Action rejects claim 11 for over broad, since the use of TRAP assay to identify other peptides is allegedly insufficient to meet the enablement requirement for those peptides because the Applicants have not provided any other structures that would predictably function in a similar manner to those of several working examples. If WO 96/19574 is enabling in terms of IL-11R inhibitor based on a generic description of a screen method which describes nothing about any structure that would function in the intended way, then the rejection to claims 2, 4, 11, 14-16, or at least claim 11, on grounds of 35 U.S.C. 112, first paragraph must be withdrawn.

Finally, regarding IL-11R antibody, aside from the reasons presented above as to why WO 96/19574 is non-enabling in general, there is an additional concern regarding this specific non-enabling embodiment. Since WO 96/19574 does not teach the regions on IL-11R that is involved in IL-11 and gp130 binding, WO 96/19574 does not enable a skilled artisan to make and use antibodies that can actually inhibit the binding between IL-11 and IL-11R, or the binding between IL-11R and gp130, without undue experimentation. The extracellular domain of IL-11R constitutes the majority of the receptor (see Figure 1 of WO 96/19574) and contains numerous potential epitopes for antibody binding. It cannot be assumed that all IL-11R antibodies, or even a majority of these IL-11R antibodies, are effective in inhibiting IL-11 / IL-11R interaction or IL-11R / gp130 interaction. In fact, generation of these antibodies requires the knowledge regarding the binding regions between IL-11R / IL-11 and IL-11R / gp130. The claimed antibodies in claims 40 and 41 are species of the genus of anti-IL-11R antibodies, since a genus does not necessarily anticipate its encompassed species, WO 96/19574 cannot anticipate claims 40 and 41. The Office Action alleges that claim 4 is too broad by reciting "mutant IL-11R," and is only enabled to the extent that the binding region is identified. The Office Action also alleges that claim 16 is too broad by reciting "IL-11R binding peptide," because one of skill would not know which binding peptides to use for inhibiting the formation of ternary complex. If a generic IL-11R antibody is enabling, then claims 2, 4, 11, 14-16, or at least claims 4 and 16 should also be enabling, and rejections of these claims on grounds of 35 U.S.C. 112, first paragraph must be withdrawn.

The Office Action further alleges that WO 9619574 teaches a variety of biological activities of the human IL-11R that would anticipate use of such IL-11R as antagonists of IL-11 binding to IL-11R (2nd para. Of page 9 to 3rd para. Of page 10), and points out instances where such inhibition may be beneficial as in treatment of postmenopausal osteoporosis. These allegations of the Office Action are based on the assumption that soluble IL-11R may serve as competitive inhibitors of IL-11 binding to its natural receptors (IL-11R / gp130) on cell surface. However, these seemingly reasonable predictions are proven to be wrong based on data presented in Example 2 of WO 96/19574, and is further confirmed to be wrong by Example 4 of the instant specification.

In addition, contrary to the allegation of the Office Action, WO 96/19574 does not teach or suggest any role IL-11 signaling might have in bone formation, since it is the instant application

that first disclose the role of IL-11 in inhibiting osteoblast function (bone formation), while WO 96/19574 at best predicts that IL-11 signaling promotes bone resorption, a function of osteoclasts.

In summary, WO 9619574 does not anticipate the claimed invention, reconsideration and withdrawal of rejection under 35 U.S.C. 102(b) is respectfully requested.

Claim rejections under 35 USC §103(a)

Claims 1-5, 10-11, 15-16, 40 and 41 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Romas et al. (1995) in view of WO 9619574. Applicants respectfully disagree.

Pursuant to MPEP 2143, "To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the reference themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations."

Romas suggests that IL-11R is expressed on both osteoclast and osteoblast, and speculates that IL-11 might have a biological function in osteoblasts. However, Romas offers no clue as to what that biological effect might be (especially whether it is stimulatory or inhibitory). In fact, Romas only investigated the role of gp130, the common signal transducer of a number of cytokines including IL-6, IL-11, OSM, LIF, CT-1, and CNTF (see page 2582, left column, 1st paragraph), in osteoclastogenesis. The data presented only shows that IL-11 can induce osteoclastogenesis *in vitro*, but it cannot rule out the possibility that other cytokines also plays a role in osteoclastogenesis *in vivo*. In fact, it does not even establish that IL-11 plays a major role in osteoclastogenesis *in vivo*. In addition, Romas by no means hinted the unexpected discovery of the instant application that IL-11 signaling is inhibitory (rather than stimulatory) in osteoblast.

WO 96/19574 presents data indicating that soluble IL-11R can promote (rather than inhibit) IL-11 signaling by stimulating proliferation of at least BAF 130-9 cells. Thus, even for the sake of argument, a skilled artisan combines the teaching of Romas and WO 96/19574, the

combined reference still does not teach or suggest the claimed invention. In fact, the combined teaching *teaches away* from the claimed invention. This is because a skilled artisan, without knowing any prior example of IL-11 signaling being inhibitory in certain cells such as osteoblasts, would only reasonably assume that IL-11 signaling stimulates cell proliferation. Since IL-11R receptor is present on both osteoclast, which is responsible for bone resorption, and osteoblast, which is responsible for bone formation, the combined teaching is not at all clear as to the possible outcome of IL-11 signaling *in vivo*. Based on the combined teaching, it is even possible that inhibiting IL-11 may depress the function of osteoblast to a greater extent than that of osteoclast, resulting in a net bone loss.

In addition, in view of Nandurkar et al. (Blood 90: 2148-2159, 1997, provided as **Exhibit B** in the reply to the previous Office Action), a skilled artisan would further doubt the *in vivo* role of IL-11 signaling in osteogenesis. Accordingly, Applicants submit that at least one of the three requirements for establishing a *prima facie* case of obviousness is not met, reconsideration and withdrawal of rejection under 35 U.S.C. 103(a) are respectfully requested.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,

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